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Ectrodactyly and Absence (Hypoplasia) of the Tibia: Are There Dominant and Recessive Types?

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We present a kindred of brother, sister, and cousin with ectrodactyly and hypoplasia of the tibia. The parents of the cousin are consanguineous; the parents of the sibs originate from the same small Algerian village. We also report on a boy with tibial defect and split hands and feet with consanguineous parents. These observations are further hints for an autosomal recessive type of ectrodactyly with aplasia (hypoplasia) of the tibia, as was favoured by some authors. However, review of the present and reported cases does not demonstrate any clinical differences between the seemingly recessive and the dominant types. Statistical analysis of 17 families with affected sibs and normal parents showed a 1:3.1 ratio of affected:unaffected by the proband method. Despite consanguinity among nine sets of parents, this ratio, and ~30 additionally reported families generally are in favour of autosomal dominance with reduced penetrance.

KEY WORDS: ectrodactyly, aplasia/hypoplasia of tibia, mode of inheritance

INTRODUCTION

Absence of tibia combined with ectrodactyly is a rare malformation with highly variable manifestations that vary from virtually no malformation to syndactyly of fingers 2/3 of one hand, tetramelic ectrodactyly with or without hypo- or aplasia of the tibia, to tetramelic monodactylous limbs with absent tibiae [Majewski et al., 1985]. Familial occurrence is not uncommon, but the mode of inheritance is not clear. In a previous paper, Majewski et al. [1985] favoured autosomal dominant inheritance with highly reduced penetrance. However, Kohn et al. [1989] argued for autosomal recessive inheritance in two consanguineous families. Here, we present observations on a consanguineous couple with an affected boy and a further healthy couple with two affected children and an affected nephew from a consanguineous mating.

CLINICAL REPORT

The parents are healthy and not known to be consanguineous, but they originate from the same small Algerian village. They have two healthy and two affected children (III-3 and III-5; Fig. 1). One pregnancy was lost for unknown reason. An affected maternal nephew (III-45; Fig. 1) has consanguineous parents. Seven healthy sibs of the mother and their 39 children are unaffected (Fig. 1).

Patient 1 (III-5)

The propositus, a 2-month-old boy, is healthy except for malformations of his lower limbs and capillary hemangioma of the forehead and neck, (Fig. 2a). Hands are unremarkable. Left foot: the hallux appears fingerlike and is displaced proximally by ~ 1 cm and separated from the two lateral rays by a deep cleft. The terminal phalanx of the hallux is bowed laterally (Fig. 2). Right foot: Toes 3–5 are present and separated from the fingerlike hallux by a deep cleft. The right hallux is very similar to the left. All toe nails are normal. There is a bilateral rocker bottom foot deformity. On radiological examination the tibiae are short and somewhat hypoplastic. The fibulae are thicker than usual and 0.5 cm longer than the tibiae (Fig. 3). In the left foot, the first metatarsal is hypoplastic, bearing one very small phalanx, only. The second toe is absent; however, the second metatarsal is present. There are only two lateral rays with hypoplastic phalanges. In the right foot, there are four metatarsals, the two medial ones being hypoplastic and the second bearing no toe. The phalanges of toes 3–5 are hypoplastic.

Patient 2 (III-3)

Both hands and the left foot are normal. The right foot shows the same malformation as the left foot of the younger brother with talipes equinus and two lateral rays only; the malformed and proximally displaced hallux was removed (Fig. 4). This 11-year-old girl has congenital deafness, but is otherwise healthy.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

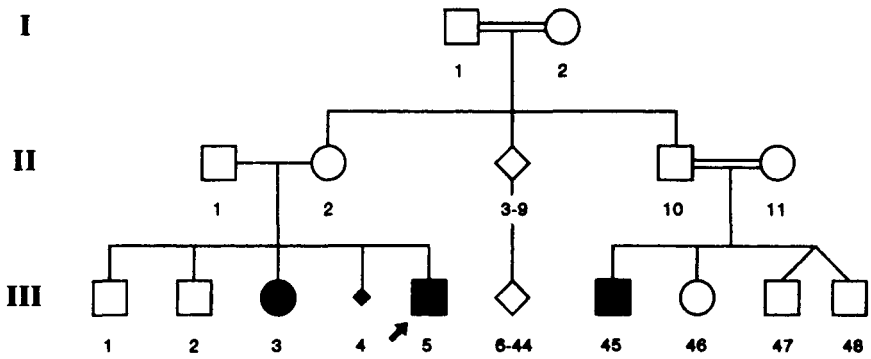

Fig. 1. Pedigree of the Algerian family.

X-ray examination before surgery showed only four right metatarsals. Both medial metatarsals were hypoplastic, the first bearing one hypoplastic distal phalanx, only, the second toe was absent. Rays three and four (or four and five) presented with normal metatarsals, but hypoplastic phalanges. The right tibia was 2 cm shorter than the somewhat broad fibula and hypoplastic.

Patient 3 (III-45)

The cousin (Fig. 1) lives in Algeria and was examined by photos only. The face is normal; he has split hands lacking ray three on the right and rays two and three on the left. The right forefoot is probably amputated (this food was said to have been rotated dorsally). The left shows the same malformations as the left foot of patient 1 (Fig. 5).

Patient 4

The healthy parents are first cousins originating from the Syrian border of Turkey. Their family history was unremarkable with respect to hand and foot anomalies. The 11-month-old propositus is a pleasant, intelligent boy with normal face but malformed limbs. The left arm was normal, but the right hand showed the typical split hand anomaly with three rays. The lower limbs were somewhat shorter than normal and severely malformed with flexion contractures at knees, hypoplastic legs, and marked club foot deformity bilaterally. His split feet showed two rays only (Fig. 6).

Radiologically, the right hand showed the split hand malformation with three rays only, the first one being slightly hypoplastic (Fig. 7). Aside from flexion deformity at both knees, the lower limbs (Fig. 8) showed forking of the distal right femur and absent tibiae. Both deformed feet demonstrated a deficiency with two rays on the right but three metatarsals on the left, two of them being "fused" distally, and two toes only.

DISCUSSION

As noted above, the variability of ectrodactyly and aplasia of the tibia is great. This variability is well demonstrated by our three patients. In patient 2, one

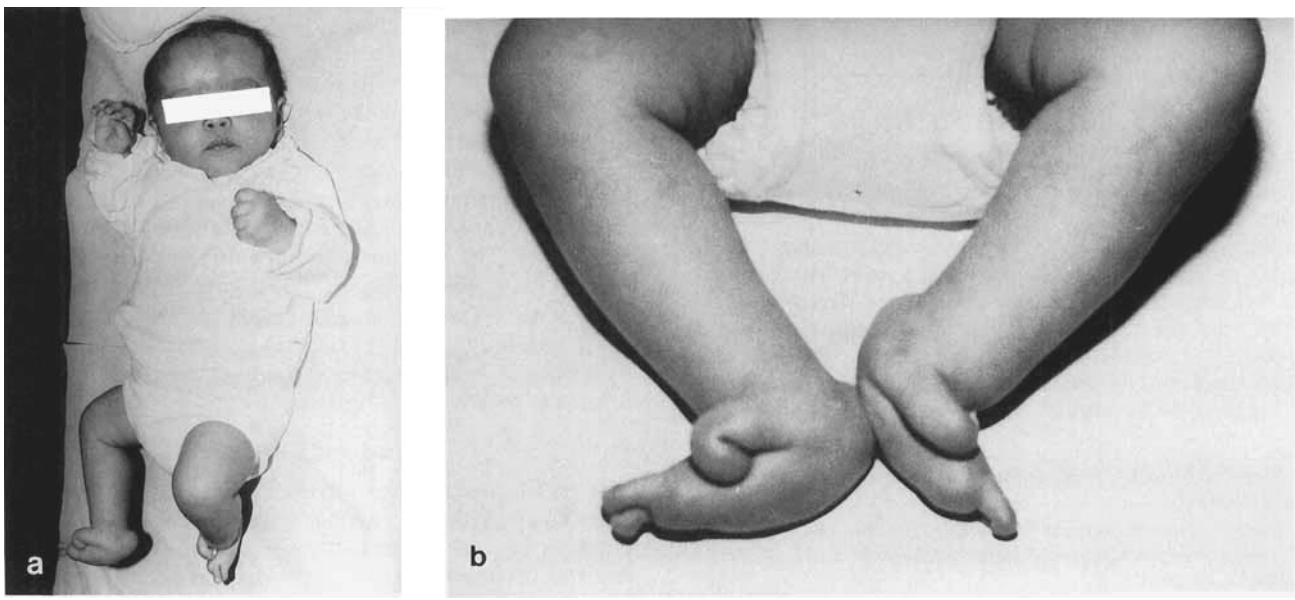

Fig. 2. **a:** Aspect of patient 1, note split feet. **b:** Legs of patient 1.

Fig. 3. Roentgenogram of legs of patient 1; note short and hypoplastic tibiae.

leg was affected by ectrodactyly only, the corresponding tibia being moderately hypoplastic and shortened. In patient 2, both legs were affected, whereas in patient 3 there was tetramelic ectrodactyly. In the most reported affected families, this was an autosomal dominant trait with reduced penetrance, as shown, e.g., by the large pedigree published by Majewski et al. [1985]. However, the same authors published on a consanguineous and healthy couple from Syria, who had three affected children.

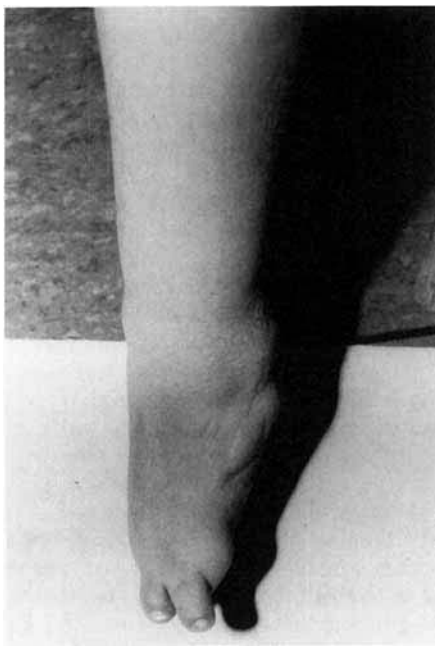

Fig. 4. Right foot of patient 2; first toe was removed surgically.

Fig. 5. Aspect of patient 3. Note split hands bilaterally, split foot left, and amputated right forefoot.

A total of 17 families with 39 affected sibs and normal parents have been described [White and Baker, 1888; Schwarzweller, 1939; Takahashi et al., 1968; Emami-Ahari and Mahloudji, 1974; Fried et al., 1977; Gollop et al., 1980; Kapur et al., 1982; Lenz, 1982; McKay et al., 1984; Majewski et al., 1985; Richieri-Costa et al., 1987b,c; Mufti and Wood, 1987; Kohn et al., 1989; Sener et al., 1990; this report]. Further single cases with consanguineous parents were reported by Der Kaloustian and Mnaymneh [1973], Mahloudji and Farpour [1974], Richieri-Costa [1987a], and Sener et al. [1989]. Wolfgang [1984] published a typically affected offspring of healthy Amish parents, known to be mostly consanguineous. This high rate of consanguinity might hint at a recessive type of tibial aplasia with ectrodactyly, as suggested by Kohn et al. [1989] and other

Fig. 6. Patient 4, split feet and short legs.

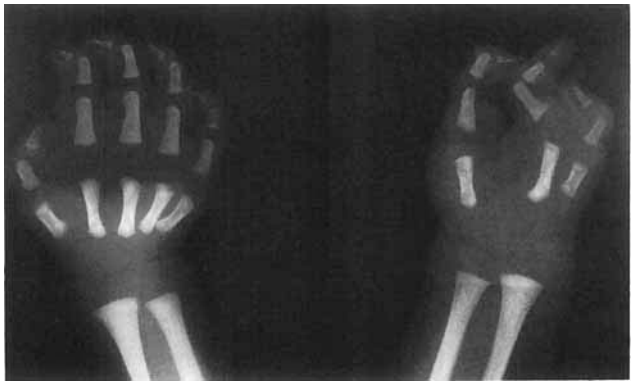

Fig. 7. Patient 4; split hand malformation with three rays in right hand.

authors. The consanguineous parents originated from Palestine [Der Kaloustian and Mnaymneh, 1973], Iran [Emami-Ahari and Mahloudji, 1974; Mahloudji and Farpour, 1974], Syria [Majewski et al., 1985], Brazil [Richieri-Costa, 1987a,c], Saudi-Arabia [Mufti and Wood, 1987], Arabia [Kohn et al., 1989], Turkey [Sener et al., 1989, 1990], and Algeria (this report). Since in all of these countries, consanguineous marriages are common, we think, in agreement with Der Kaloustian and Mnaymneh [1973], this to be only a relative weak hint for a recessive type. The variability of this malformation is high in families with seemingly horizontal transmission and in families with vertical transmission. Bifurcation of the distal femur was observed in both types of families [i.e., Kohn et al., 1989; Majewski et al., 1985, family 4]. There is no single combination of anomalies that exclusively occurs in the "recessive" or "dominant" variant.

Within the 17 families with seemingly horizontal transmission, there were 39 affected (19 females, 20 males) and 44 unaffected sibs. After correction by the proband method, the ratio of affected:unaffected is 21:65 = 1:3.1. Using the method of Finney [1947/49] in the version of Kaelin [1955], a segregation ratio of

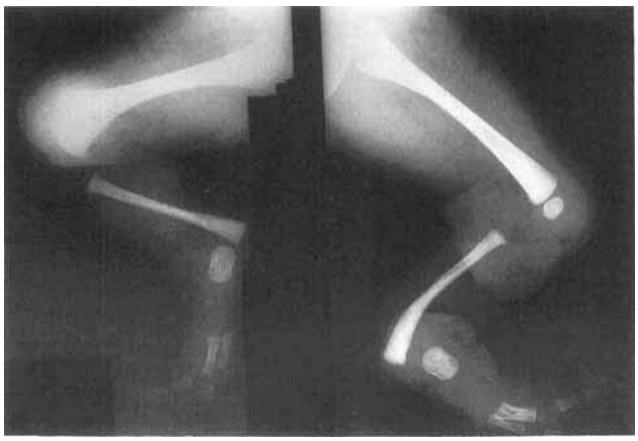

Fig. 8. Patient 4; absent tibiae and forking of the distal right femur, split feet with only two and three rays, respectively.

$P = 0.323 \pm 0.054$ (K=0, single selection) and $P = 0.445 \pm 0.059$ (K=1, complete selection) is obtained with 95% confidence limits 0.218–0.428 under the assumption of single selection. Since ascertainment of the cases is very heterogeneous, no firm conclusion can be drawn from these estimates. Neither autosomal dominant nor recessive inheritance can be rejected, particularly since in the apparently dominant families reduced penetrance was shown. This was demonstrated by the large pedigree of family 1 of Majewski et al. [1985], as well as four pedigrees published by Hoyme et al. [1987], and some others with an apparently autosomal dominant pattern. In 1985, we estimated the penetrance to be in the order of 60%, but exact calculation is not possible, since ascertainment and description of the literature families are very variable.

An interesting family was reported by Yelton [1962]. A normal man had three affected children from three healthy and nonrelated wives. This could be explained by germinal mosaicism, or by reduced penetrance of a dominant gene. Schwarzweller's family was restudied by ter Haar (pers. comm.); after the original report a further affected boy had been born. The six affected sibs together had 32 children, one of which was also affected. The parents of the affected girl were nonconsanguineous through at least six generations. By this affected child, the pedigree is no more an example for a "recessive variant," but for a dominant with reduced penetrance. The same is likely for the pedigree noted by Mahloudji and Farpour [1974], as well as for the pedigree noted by Mufti and Wood [1987]. In the latter family, the unaffected father had four affected girls from two unaffected wives; he was consanguineous with one wife, but not with the second. The parents of the propositus of Sener et al. [1989] were consanguineous, but two affected relatives indicate dominant inheritance with reduced penetrance. In a further pedigree [Sener et al., 1990], a consanguineous unaffected couple had two affected sons and three normal daughters. This is in favour of recessive genes. But both grandfathers (who were brothers) were affected, as well as a brother of the mother and a nephew of the father. Since the parents of all further affected persons were not known to be consanguineous, pseudo-dominance of a recessive trait seems unlikely. This pedigree could be explained more plausibly on the basis of reduced penetrance of a dominant gene.

The same discussion on the existence of a recessive variant existed for isolated split hand/split foot (SHSF) [for a summary see Mufti and Wood, 1987]. Zlotogora et al. [1994] analyzed most of the reported pedigrees with isolated (type I) and syndromal (type II) SHSF malformation. Isolated SHSF clearly was caused by an autosomal dominant gene with high penetrance (96%), but the authors did not divide the pedigree into two categories: one type with regular dominant transmission and involvement of hands and feet, and one type with irregular dominant transmission and inconstant involvement of the feet. In the latter type, the hands often are affected asymmetrically [Bujdoso and Lenz, 1980; Viljoen and Beighton, 1984; Lenz and Majewski, 1991]. The first type is highly penetrant, whereas penetrance

in the second type is ~50%. Type II of SHSF (plus other limb involvement) seems to be heterogenous; therefore, the calculation of penetrance is very uncertain.

Genuardi et al. [1993] observed a family with SHSF and a balanced translocation including the breakpoint 7q22.1. Since one child in this family presented with tibial hypoplasia and other authors observed translocations with the same breakpoint in families with isolated SHSF, the gene(s) for isolated and "syndromal" SHSF both are postulated to be on chromosome 7q22.1. This locus is called SHSF1. Since some families with SHSF show no linkage to this locus, heterogeneity is probable.

Until the gene(s) are identified, the question remains open whether a dominant and recessive form of SHSF with a(hypo)plasia of tibia exist and therefore genetic counseling in healthy sibs of affected is difficult in isolated SHSF and in aplasia of tibia with SHSF. In both cases, there may be a recurrence risk to offspring of up to 25%.

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